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ORIGINAL RESEARCH **INTENSIVE CARE**

Effect of neuromuscular electrical stimulation on renal functions in pregnancy related acute kidney injury: a randomized controlled trial

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Abstract

Background: Various therapies have been used to restore blood flow and stabilize renal function in patients with pregnancy related acute kidney injury (AKI-P). There are favorable effects of electrical stimulation on muscle metabolism, microcirculation and possibly renal function; therefore, this study suggests for the first time that neuromuscular electrical stimulation (NMES) has a positive effect on renal functions of women with AKI-P.

Methods: This randomized controlled design study evaluated the effect of NMES on renal blood flow and hemodynamics for women with AKI-P. Patients were randomized into two groups; NMES group (Group ES) versus Control group (Group C). Group ES received routine care and NMES while Group C received routine care only, data was collected from obstetric ICU. Improvement of renal functions was considered the primary outcome and secondary outcome was improvement of hemodynamics.

Results: NMES application had caused no a statistical significant change in serum creatinine in Group ES than Group C on mid period and last day of the study (230.13 ± 83.69 in Group ES versus 258.3 ± 115.77 in Group C) and (180.21 ± 63.65 in Group ES versus 201.32 ± 84.78 in Group C) (P = 0.285 & P = 0.297) respectively.

Conclusion: Application of NMES had no effect on their renal functions but there are improvements on hemodynamics.

Trial registration: The study registered in Clinical-Trials.gov at 8 October 2020 - prospectively registered, http://www. Clinical- Trials.gov.com/ NCT04580329

Abbreviations: CVP: Central venous pressure; ES: Electrical stimulation; GCS: Glasgow coma scale; HR: Heart rate; MAP: Mean arterial pressure; NMES: Neuromuscular electrical stimulation; AKI-P: Pregnancy related acute kidney injury; RR: Respiratory rate

Key words: Neuromuscular electrical stimulation; Acute kidney injury; Renal functions

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1. Introduction

Pregnancy related acute kidney injury (AKI-P) is a challenging health problem in pregnant women, especially in the developing countries. The incidence of AKI, complicating pregnancy and requiring dialysis, is approximately one in 20,000 births in industrialized countries. Pregnancy is has been responsible for 15–20% of total AKI cases in the various developing countries.[1]

AKI is defined when one of the following criteria is met; serum creatinine rises by 26 µmol/L within 48 h, or serum creatinine rises 1.5 fold from the reference value, which is known or presumed to have occurred within one week or urine output is < 0.5 ml/kg/h for > 6 consecutive hours.[2]

In AKI there is a marked reduction in corticomedullary blood flow, which leads to significant reductions in glomerular filtration rate (GFR) during early phases of the disease. The recognition that hypo-perfusion of the outer medulla is common to many forms of AKI and contributes to tubular ischemia has led many investigators to use various therapies to restore blood flow and stabilize renal function.[3]

Neuromuscular electrical stimulation (NMES) is a procedure in which small electric impulses are used to stimulate muscles that are weak or paralyzed.[4] It helps to increase muscle strength, blood circulation, and range of motion and to lessen muscle spasms. There is increasing use of NMES as an antiemetic and for restoration of blood flow to ischemic tissue and wounds. NMES has been used in patients suffering from chronic obstructive pulmonary disease and heart failure.[4] As patients suffering from AKI, and on hemodialysis, present similar symptoms of other chronic diseases that directly affect the functional capacity, the use of NMES could be beneficial to them.[4]

NMES modulates the local, and possibly the systemic microcirculation. It increases the blood flow in the intact skin as well as of chronic ulcers of the lower legs.[5] Impressive circulatory effects were observed after chronic spinal cord stimulation in patients with severe coronary heart disease,[5] as well as in critical lower limb ischemia.[6]

Also NMES of the thighs increases the blood flow of the lower limbs.[7] In line with these circulatory effects, NMES of the thighs enhances GFR and fractional sodium excretion in healthy subjects.[8]

In light of these potentially favorable effects of electrical stimulation of muscle metabolism, microcirculation and possibly renal function, we conducted this study that to confirm that whether NMES has a positive effect on the renal functions of patients with pregnancy AKI-P or not.

2. Methodology

The project was reviewed and approved by the Medical Ethics Committee in the faculty of Medicine in Assiut University in Egypt (IRB No.: 17300485) and registered in ClinicalTrials.gov at 8 October 2020 (NCT04580329), and has been performed in accordance with the ethical standards of the Declaration of Helsinki. This study adheres to CONSORT guidelines. Figure 1 presents the CONSORT flowchart. Written informed consent was obtained from all patients prior to their inclusion in the study.

Improvement in the renal function was considered as the primary outcome and the improvement in the hemodynamic parameters as the secondary outcome. Data was collected from obstetric ICU.

The inclusion criteria were: post-partum women, who developed AKI in the puerperal period (the first six weeks following childbirth), aged 18 y or older and hemodynamically stable. Patients who required any emergency or elective surgery during the study; those who presented acute heart or lung disease, skin rashes, tumors, infections, diabetes mellitus or hypoesthesia in the region that the neuromuscular electrical stimulation was to be applied, were excluded. Patients with a pacemaker, epileptic patients, patients with recent effects of stroke (less than 3 months) and uncontrolled hypertension (systolic blood pressure > 230 mmHg and diastolic blood pressure > 120 mmHg) were also excluded.

We hypothesized that renal functions and hemodynamics in post-partum women with AKI-P will be significantly improved after application of NMES.

A power calculation to detect an effect size of 2.5, difference in mean of serum creatinine between the two studied groups, with a $P < 0.05$ and 80 % power, confidence level 0.95, a sample size of 27 patients for each group was needed. However, 60 patients (30 for each group) were included in this research to cater for the drop outs. This calculated using G Power 3.1 [9].

Eligible patients were randomized into two groups: control group (Group C) and neuromuscular electrical stimulation group (Group ES) through data generated by random.org online software. The sequence of numbers was generated by researchers ‘blind’ to the study after the selection of patients for eligibility criteria and disclosed prior to the start of the intervention program.

In the Group ES, NMES was applied through a calibrated electrical stimulator (Neurodyn II®, model N53, IBRAMED™), using rectangular symmetrical biphasic pulsed current. NMES session was applied to the patient in a supine position as two hypoallergenic, self-adhesive electrodes (VALUTRODE - 9 × 5 cm) were placed in

parallel on retroperitoneal site in both sides, 6 cm apart and four electrodes were placed simultaneously on the motor point of the quadriceps muscle and perpendicular to the longitudinal axis of the thigh and above the upper border of the patella in both lower limbs. NMES was applied for three sessions per week for two weeks and each session take 55 min, including 5 min for warm up and 5 min for recovery, at 80 Hz frequency, 400 µsec pulse width, and 10 sec contraction time. The intensity (amplitude) was increased until the patient was able to feel a strong but comfortable tingling sensation. Patients were asked about the intensity of the NMES every 10 min. The NMES intensity was adjusted to obtain a visible muscular contraction and, in case of doubt, the contraction was confirmed by palpation of the involved muscles. The procedure was done in the obstetric ICU.

Table 1: Distribution of personal and medical data related to the two studied groups

Personal and medical data	NMES N (%)	Control N (%)	P
Age group			
Less than 30 year	13 (43.3)	15 (50.0)	0.667
from 30−40 years	13 (43.3)	13 (43.3)	
More than 40 years	4 (13.3)	2 (6.7)	
Mean ± SD	32.87 ± 7.1	30.87 ± 6.08	0.246
ICU stay days			
Less than 5 days	18 (60.0)	8 (26.7)	
from 5−10 days	11 (36.7)	19 (63.3)	0.030*
More than 10 days	1 (3.3)	3 (10.0)	
ICU stay days	5.6 ± 3.14	7.83 ± 3.66	0.014*

*Chi square test for qualitative data between the two groups, independent t-test for quantitative data between the two groups, **significant level at P < 0.01*

Figure 1: Neurodyn II, model N53, IBRAMED machine used in the study

To evaluate renal functions, urine output was measured every hour and total input and output was evaluated and compared before and after NMES application for Group ES and routinely for Group C. Serum creatinine level, serum sodium and serum potassium were measured after 48 h of each NMES session for Group ES and routinely for Group C.

The hemodynamic parameters were monitored by 24 h cardiac monitor to perform a continuous recording of blood pressure, heart rate, and oxygen saturation over 24 h. All data was recorded on a digital recorder, with subsequent analysis being carried out by trained professionals. Skin temperature was measured using a thermistor probe placed under axilla for five min, and oxygen saturation was monitored by pulse oximetry.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA. Continuous variables are presented as mean ± SD, and categorical variables, as frequencies. Differences between the groups at baseline were evaluated by an

unpaired t test or the Mann–Whitney test for comparison of continuous variables. The Chi-square test or Fisher's exact test was employed to compare categorical variables. Analyses were performed by comparing baseline and post intervention variables in the subgroups (Group ES vs. Group C).

3. Results

Seventy patients with AKI-P in obstetric ICU were evaluated according to the eligibility criteria and 60 patients were included in the study.

Personal and medical data of the patients in the two groups were evaluated. Results showed that there were no significant statistical differences between the two groups in relation to socio-demographic data and medical characteristics ($P > 0.05$) except ICU stay in which there was a highly significant difference ($P = 0.002$) (Table 1 & Figure 2).

The application of NMES didn't show any significant change on heart rate and body temperature ($P > 0.05$), whereas there was a significant increase in MAP within the Group ES [(94.57 ± 15.74 mmHg) on the first day of the study and (90.17 ± 13.34 mmHg) on mid period of the study] than Group C [(84.47 ± 16.35 mmHg) on the

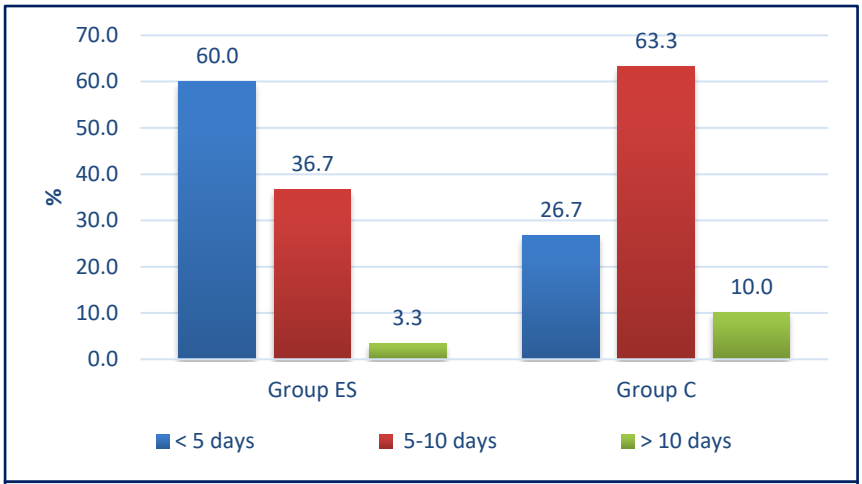

Figure 2: Comparison between Group ES and Group C related to ICU stay

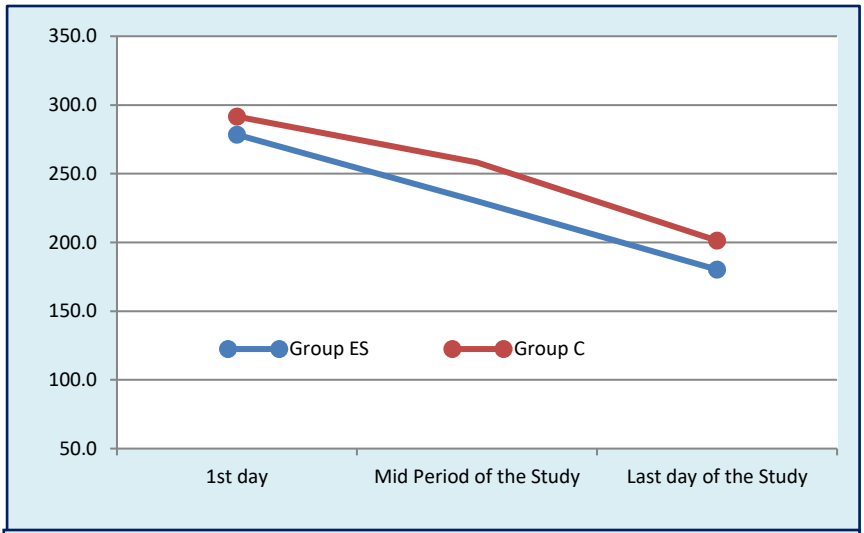

Figure 3: Comparison between Group ES and Group C related to serum creatinine

first day of the study and (83.57 ± 10.68 mmHg) on mid period of the study (P < 0.05)]. In addition, NMES didn't result any significant change on GCS (P > 0.05). Also, there was a significant effect of NMES on CVP on the first and last days of the study (P < 0.05) (Table 2).

The application of NMES shows significant change on serum sodium and serum creatinine (P-value < 0.05). NMES application had not caused any a statistical significant change in serum creatinine in Group ES than Group C on mid period and last day of the study as in Figure 3 (230.13 ± 83.69 in Group ES versus 258.3 ± 115.77 in Group C) and (180.21 ± 63.65 in Group ES versus 201.32 ± 84.78 in Group C) (P = 0.285 & P = 0.297) respectively (Table 2).

Also NMES application shows a high statistically significant change on urine output and fluid balance; as regard to urine output there was significant change on the first and after three days of the study (P = 0.002 & P = 0.001 respectively), as regard to fluid balance there was a high statistically significant change all over the period of the study (P = 0.010, P = < 0.001, P = 0.001 respectively) (Table 3).

4. Discussion

In normal functional muscle, regular muscular contractions act to facilitate regional blood flow by 'pumping' blood through the vascular network. NMES induces repeated muscular contraction, possibly promoting the perfusion/oxygenation of the regional tissues. It remains unclear how NMES influences vascular hemodynamic property and segmental fluid distribution/composition in patients with AKI-P but animal studies demonstrate increased microvascular perfusion with transcutaneous NMES.[10–13]

The ability of NMES to impact peripheral vascular resistance and cause a transient local increase in blood flow is dependent on stimulation intensity.[14] The impact of NMES on peripheral hemodynamic functioning is the focus of several studies.[15–19] In one study there was a linear increase in femoral arterial blood flow with increasing stimulation rates of NMES.[20]

Validating the efficacy of NMES as an adjuvant technique for improving tissue perfusion and blood flow is an important opportunity to improve the outcomes of post-partum women with AKI-P. To the best of our knowledge, this is the first study to examine the effect of NMES application on postpartum women with AKI-P.

One of the main findings of this study was that an NMES session result in change in hemodynamic parameters as MAP, RR, and CVP in patients in the first and mid period of study for MAP and in the first and last day of the study for RR and CVP; there were no significant changes observed in HR and temperature.

Table 2: Comparison between Group ES and Group C related to hemodynamic parameters

Parameters		Group ES	Group C	P
Temperature	1st day of the study	37.61 ± 0.57	37.51 ± 0.47	0.461
	Mid period of the study	37.31 ± 0.35	37.3 ± 0.54	0.955
	Last day of the study	37.24 ± 0.32	37.27 ± 0.46	0.771
Heart rate (HR)	1st day of the study	109.93 ± 23.26	101.23 ± 21.6	0.139
	Mid period of the study	97.1 ± 16.65	100.37 ± 20.24	0.497
	Last day of the study	95.79 ± 18.88	97.43 ± 20.15	0.754
Mean arterial pressure	1st day of the study	94.57 ± 15.74	84.47 ± 16.35	0.018*
	Mid period of the study	90.17 ± 13.34	83.57 ± 10.68	0.039*
	Last day of the study	84 ± 12.54	81.71 ± 12.33	0.495
Resp. rate (RR)	1st day of the study	21.93 ± 4.46	19.40 ± 6.31	0.078
	Mid period of the study	18.83 ± 4.19	19.7 ± 6.82	0.556
	Last day of the study	15.82 ± 3.24	19.64 ± 6.84	0.010*
CVP	1st day of the study	17.07 ± 5.9	14.53 ± 4.52	0.067
	Mid period of the study	14.4 ± 3.72	14.7 ± 4.88	0.790
	Last day of the study	13.21 ± 3.83	16.46 ± 6.32	0.024*
GCS	1st day of the study	14.83 ± 0.46	14.93 ± 0.37	0.356
	Mid period of the study	15 ± 0	15 ± 0	-
	Last day of the study	15 ± 0	15 ± 0	-
White blood cell count	1st day of the study	17.67 ± 7.5	15 ± 7.98	0.187
	Mid period of the study	12.75 ± 5.11	15.55 ± 7.33	0.092
	Last day of the study	9.75 ± 3.5	15.21 ± 7.4	0.001**
Serum sodium	1st day of the study	137.98 ± 5.23	136.73 ± 4.82	0.339
	Mid period of the study	137.19 ± 3.43	138.48 ± 4.76	0.235
	Last day of the study	136.37 ± 3.89	138.61 ± 4.25	0.044*
Serum potassium	1st day of the study	3.89 ± 0.51	4.09 ± 0.82	0.263
	Mid period of the study	3.74 ± 0.57	4.06 ± 0.8	0.082
	Last day of the study	3.93 ± 0.54	3.99 ± 0.7	0.715
Serum creatinine	1st day of the study	278.37 ± 91.29	291.55 ± 151.6	0.685
	Mid period of the study	230.13 ± 83.69	258.3 ± 115.77	0.285
	Last day of the study	180.21 ± 63.65	201.32 ± 84.78	0.297

- Independent t-test for quantitative data between the two groups
*- *significant level at P < 0.05, **significant level at P < 0.01.*
- Mid period of the study is after 7 days of the treatment. Data presented as Mean ± SD

In the past, many professionals worked with NMES in critical ill disease to evaluate its effect on cardiovascular system. A previous study found that a session of NMES in critically ill patients increased the SBP by 6 mmHg and the HR by 5 bpm, respectively, although the authors stated that this result was not clinically significant.[19] Another author also found small changes in HR, of approximately 1 bpm, and in SBP and DBP, of approximately 1 mmHg, with no statistical significance when NMES was applied on the femoral quadriceps of critically ill patients.[21] These borderline increases in BP after the use of NMES in critically ill subjects are in agreement with the results presented by the present study, and it is in contrast to the effect on HR.

In contrast to the present study, another study has shown that NMES induced energy expenditure and

Table 3: Comparison between Group ES and Group C related to total intake and total output and fluid balance

Parameter	Group ES	Group C	P
Total intake			
1st day of the study	3243.33 ± 2081.77	3190 ± 1607.23	0.912
Mid period of the study	2683.33 ± 1122.45	2668.33 ± 1037.86	0.957
Last period of the study	2563.33 ± 1525.36	2591.67 ± 1487.02	0.942
Total output			
1st day of the study	2950 ± 2108.48	1470 ± 1388.04	0.002**
Mid period of the study	3303.33 ± 1334.94	2008.62 ± 1404.88	0.001**
Last period of the study	3060 ± 1475.86	2222.33 ± 1797.84	0.053
Balance			
1st day of the study	280 ± 1952.66	1720 ± 2247.93	0.010*
Mid period of the study	−603.33 ± 1170.47	753.33 ± 1510.89	< 0.001**
Last period of the study	−336.67 ± 1121.95	661.33 ± 992.77	0.001**

- Independent t-test for quantitative data between the two groups
*- *significant level at P < 0.05, **significant level at P < 0.01*
- Mid period of the study is after 7 days of the treatment. Data presented as Mean ± SD

cardiovascular response similar to other types of exercise in other patient profiles, with higher HR increases.[22]

Electrical stimulation (ES) has been shown to increase cutaneous perfusion in human studies. Thereafter, over a period of 30–40 y, a great deal of information has been produced that has laid out the basis of current

understanding of how the renal sympathetic innervation affects all aspects of renal function. A number of major reviews of the anatomy, physiology, and pharmacology of the sympathetic innervation of the kidney appeared in the 1990s and early 2000s, which have brought together which have brought together the most significant pieces of information about the renal sympathetic nerves at the time.[23–24]

There are findings that appear to support the hypothesis that use of ES as NMES using implanted systems can increase regional blood flow, decrease urinary albumin secretion and improve renal blood flow and GFR in nephropathy patients and animals. These findings can explain the results of our study which show that there was slight improvement in serum creatinine after treatment in the mid period and on last day of the study.

A study by Poucher SM and Karim F clearly showed that significant changes in renal tubular function could occur in the absence of changes in renal blood flow and GFR when the renal nerves were stimulated electrically from a baseline activity up to a frequency of 1.5 Hz. Higher frequencies caused significant changes in both renal hemodynamics and the function.[22] This finding is in line of the results of the current study.

DiBona and colleagues, using the rat, analyzed the strength-duration relationship during direct electrical renal nerve stimulation in relation to renal blood flow and urine flow and sodium excretion, and found a higher stimulation threshold for the nerve fibers involved in

regulating renal blood flow compared to those involved in regulating fluid excretion.[25] It supports the results of our study which show that there was light improvement in urine output and serum creatinine in Group ES than Group C.

5. Limitation

The study involved relatively a small sample size, and the control group was not case-matched.

6. Conclusion

It can be concluded that application of neuromuscular electrical stimulation for post-partum women with pregnancy related acute kidney injury had no significant effect on their renal functions but there was improvement in their hemodynamic parameters.

7. Ethics approval and consent to participate

The project was reviewed and approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University in Egypt (IRB No: 17300485) and has therefore been performed in accordance with the

ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to their inclusion in the study.

8. Availability of data

The data sets used and/or analyzed during the current study are available from the authors on reasonable request.

9. Conflict of interests

The authors report there are no competing interests to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

10. Acknowledgements

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11. Authors' contributions

AT & AS analyzed and interpreted the patient data and were the main contributors in writing the manuscript.

II & AM performed the clinical examination of the patients and had a major role in data collection. All authors have read and approved the final manuscript.

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